Food and Drug Administration Briefing Document
Oncologic Drugs Advisory Committee Meeting
June 20, 2012

New Drug Application (NDA) 202714
Carfilzomib (Kyprolis)
Applicant: Onyx Pharmaceuticals

Proposed Indication: Treatment of Relapsed or Refractory Multiple Myeloma

DISCLAIMER STATEMENT

The attached documents contain background material prepared by the Food and Drug Administration (FDA) for the panel members of the Advisory Committee (AC). The FDA background package often contains assessments and/or conclusions and recommendations written by individual FDA reviewers. Such conclusions and recommendations do not necessarily represent the final position of the individual reviewers, nor do they necessarily represent the final position of the Review Division or Office. We are presenting the carfilzomib NDA with the Applicant's proposed indication, "the treatment of patients with relapsed and refractory multiple myeloma who have received at least 2 prior lines of therapy that included a proteasome inhibitor and an immunomodulatory agent" to this Advisory Committee in order to gain the Committee's insights and opinions. This background package may not contain all issues relevant to the final regulatory recommendation and instead is intended to focus on issues identified by the Agency for discussion by the advisory committee. The FDA will not issue a final determination on the issues at hand until input from the advisory committee process has been considered and all internal reviews have been finalized. The final determination may be affected by issues not discussed at this meeting.

This document is based on the Applicant's original NDA submission and subsequent information as provided up to March 15, 2012.

All tables are from Food and Drug Administration analysis unless otherwise stated.

1. Introduction

On November 26, 2011, Onyx Pharmaceuticals submitted a New Drug Application (NDA) for carfilzomib for the treatment of patients with relapsed or refractory multiple myeloma. This application is based upon the results of Study PX-171-003 Part 2 (Study 3), a Phase 2 single-arm trial that enrolled 266 patients with refractory or relapsed multiple myeloma who received at least 2 prior lines of therapy that included a proteasome inhibitor and an immunomodulatory agent (IMiD). Data from several other Phase 1 and 2 trials was included in the submission.

Issues in the review of this application, for which the Food and Drug Administration (FDA) seeks advice from the Oncology Drug Advisory Committee (ODAC) include the following:

- Do the efficacy results provide sufficient evidence that carfilzomib provides a benefit over available therapy for patients with relapsed/refractory multiple myeloma?
- Does the evidence submitted in the NDA clarify which patients with relapsed/refractory multiple myeloma are at high risk of life threatening toxicities of carfilzomib?

2. Background

Carfilzomib

Carfilzomib is a second-generation proteasome inhibitor. Carfilzomib consists of an epoxyketone pharmacophore attached to a tetrapeptide backbone. The epoxyketone pharmacophore of carfilzomib forms an irreversible, covalent bond functioning as an inhibitor of the chymotrypsin-like activity of the 20S proteasome, the proteolytic core particle within the 26S proteasome complex, when carfilzomib is given in a dose range of 20 to 27 mg/m^2. Following the irreversible binding of carfilzomib to the 20S proteasome, proteasome activity is restored through cellular synthesis of new proteasome proteins.

Non-Clinical Studies

Significant cardiac, gastrointestinal, renal and pulmonary toxicities were observed in rats and monkeys receiving bolus intravenous injections of carfilzomib. Monkeys administered a single bolus intravenous dose of carfilzomib at 3 mg/kg (approximately 1.3 times the recommended dose in humans of 27 mg/m^2 based on body surface area) experienced hypotension, increased heart rate, and increased serum levels of troponin-T. The repeated bolus intravenous administration of carfilzomib at $\geq$ 2 mg/kg/dose in rats and 2 mg/kg/dose in monkeys using dosing schedules similar to those used clinically resulted in mortalities that were due to toxicities occurring in the following systems:

- Cardiovascular (cardiac failure, cardiac fibrosis, pericardial fluid accumulation, cardiac hemorrhage/degeneration),
- Gastrointestinal (necrosis/hemorrhage),
- Renal (glomerulonephropathy, tubular necrosis, dysfunction), and
- Pulmonary (hemorrhage/inflammation).

Following repeated bolus intravenous administration in monkeys at $\geq$ 1 mg/kg/dose, cardiovascular toxicities included myocardial degeneration, myocyte hypertrophy and inflammation. Other toxicities noted in rats included thrombocytopenia and an acute phase response. Many of these toxicities observed in non-clinical studies were the same ones observed in clinical studies.

The dose of 2 mg/kg/dose in rats resulted in systemic exposures (AUCs) approximately 40% of those observed in patients who received 27 mg/m^2 of carfilzomib twice weekly for two weeks.

The non-clinical safety studies in rats and monkeys were conducted with bolus intravenous injections of carfilzomib (usually over 20 seconds), while in the Applicant's primary efficacy study (Study 3), carfilzomib was administered as an intravenous bolus injection over 2 to 10 minutes. In an attempt to further reduce the toxicities observed in rats with the twice weekly bolus administration (dosing was on consecutive days; i.e., days 1, 2, 8, 9, 15, 16, etc.), a series of studies were conducted in rats comparing the pharmacodynamics, pharmacokinetics and toxicities of intravenous carfilzomib administered as a bolus injection, a 10-minute infusion or a 30-minute infusion in order to investigate the potential for reducing drug-related toxicities by reducing the peak serum concentrations. The C_{max} and significant toxicities in rats, including death, pre-renal azotemia (elevated blood urea nitrogen and creatinine), lethargy, and dyspnea observed following a single bolus injection of 8 mg/kg carfilzomib were reduced when the same dose was administered as a 30-minute infusion, while a similar level of proteasome inhibition was maintained.

Clinical Pharmacology Studies

The Applicant did not conduct a human Absorption, Distribution, Metabolism, Excretion (ADME) study; instead, excretion data were available from a rat study. The rat excretion study showed that 30.5% of the administered drug undergoes biliary elimination while about 26% of the administered drug is eliminated by the kidneys.

The Applicant conducted a renal impairment study where the pharmacokinetic (PK) and safety of carfilzomib were evaluated in patients with normal renal function and those with mild, moderate, and severe renal function and patients on chronic dialysis following carfilzomib doses of 15 mg/m^2 during Cycle 1, 20 mg/m^2 during Cycle 2, and 27 mg/m^2 during Cycles 3 and beyond. The C_{max} and AUC of carfilzomib were similar across all renal function categories following carfilzomib doses of 15 and 20 mg/m^2. PK data were not available for the proposed 27 mg/m^2 dose. The mean treatment duration for all renal function categories was 5.5 months. The safety profile of carfilzomib was similar across all renal function categories.

Pharmacokinetic data were available from 85 patients who took part in the primary efficacy Phase 2 trial in patients with multiple myeloma. Exposure-response analyses for efficacy showed that increasing doses did not result in increased efficacy. There were not sufficient data to conduct exposure-response analysis for liver toxicity.

An *in vitro* study showed carfilzomib to be a moderate CYP3A4 inhibitor. To confirm these *in vitro* PK findings, a human PK study was conducted in cancer patients following the administration of the CYP3A4 substrate midazolam in the absence and presence of carfilzomib. The C_{max} and AUC of midazolam were similar across all three time periods, indicating that carfilzomib does not influence the PK of CYP3A4 substrates.

A Clinical Pharmacology issue that is not addressed in this NDA package is that of hepatic impairment. The sponsor did not conduct a human ADME study and the rat excretion study showed 30.5% of the administered drug undergoes biliary elimination. In the primary efficacy Phase 2 study (Study 3), one of the most important adverse effects was liver enzyme elevations, where 42.1% exhibited a Grade 1-2 elevation of alanine aminotransferase (ALT) from baseline and 3.6% experienced Grade 3 ALT elevations. These findings indicate patients with baseline hepatic impairment might be at an increased risk of liver toxicity.

Clinical

Multiple Myeloma

Multiple myeloma is a malignancy of plasma cells. These cells accumulate in the bone marrow resulting in destruction of boney structures and marrow failure. Symptoms and signs of the disease include bone pain and bone damage, hypercalcemia, renal failure, and anemia. Affected individuals may also have frequent infections, weight loss, and weakness or numbness. Loss of function of visceral organs due to deposition of light chains and infiltration by neoplastic plasma cells can occur as well. Multiple myeloma is a disease primarily of older individuals.

FDA Approved Agents for Multiple Myeloma

There are 7 drugs that are currently approved for the treatment of multiple myeloma in multiple drug classes (Table 1). Six of these drugs have received full approval, while one of these drugs (thalidomide) was approved under the accelerated approval pathway and has not received full approval for multiple myeloma. Both thalidomide and lenalidomide are under restricted distribution programs. Dexamethasone is approved for the treatment of hematologic malignancies. All of these agents would be considered to be available therapy under the regulations.

Table 1. FDA Approved Drugs for Multiple Myeloma

Class	Drug	FDA Approval
Alkylating agents	Melphalan Cyclophosphamide	Full Full
Anthracyclines	Liposomal doxorubicin (Doxil™)	Full
Nitrosureas	Carmustine	Full
ImiDs	Thalidomide Lenalidomide	Accelerated Full
Proteasome Inhibitors	Bortezomib	Full

The current treatment for multiple myeloma focuses on therapies that decrease the clonal plasma cell population resulting in an improvement in the signs and symptoms of the disease. The treatment chosen for patients with multiple myeloma depends on the age and

performance status of the patient, as well as on the stage of the disease. High-dose chemotherapy with autologous hematopoietic stem-cell transplantation has become a standard treatment for patients under the age of 65 years. Conventional dose combination chemotherapy is given as initial therapy prior to the use of myeloablative therapy/autologous stem cell transplant. Common conventional dose induction chemotherapy regimens include: bortezomib-based chemotherapy regimens, thalidomide/dexamethasone-based chemotherapy regimens, and lenalidomide/dexamethasone-based chemotherapy regimens. Autologous stem cell transplantation is the most common type of stem cell transplantation used to treat patients with multiple myeloma. None of the above cited treatments are curative. Allogeneic stem cell transplantation is the only therapy for multiple myeloma that has the potential for a cure, but only a minority of patients is eligible for this treatment.

For patients over the age of 65 years with multiple myeloma and patients with significant pre-treatment organ comorbidities which would preclude the administration of any of the regimens described in the previous paragraph, treatment might include melphalan and prednisone with or without a proteasome inhibitor or an IMiD.

Recurrent Disease

In patients with multiple myeloma who have relapsed following initial therapy, the choice of subsequent treatment depends on patient specific features, disease specific features, the duration of the response to the initial therapy, and the type of therapy used in the beginning. There are no established care pathways for patients with multiple myeloma who have relapsed following initial response or who are primary refractory.

Treatment approaches for patients who have been shown to progress following a response to initial therapy include retreatment with the drugs used for the initial therapy, as well as treatment with a different conventional dose chemotherapy regimen consisting of other available agents. These agents may include bortezomib, lenalidomide, thalidomide, anthracyclines, cyclophosphamide, and melphalan. Treatment of patients with multiple myeloma who have relapsed or are primary refractory can also include a second stem cell transplant if that treatment has already been delivered and the response was significant. A final option is therapy conducted under research protocols.

Regulatory

Applicant's Proposed Indication

The Applicant's proposed indication is for *the treatment of patients with relapsed and refractory multiple myelomas who have received at least 2 prior lines of therapy that included a proteasome inhibitor and an immunomodulatory agent*. The Applicant has requested the approval of this indication on the basis of a single arm Phase 2 trial through the accelerated approval pathway.

Accelerated Approval

Accelerated approval is a regulatory pathway that applies to certain new drug products that have been studied for their safety and effectiveness in treating serious or life-threatening illnesses and that provide meaningful therapeutic benefit to patients over

existing treatments [e.g., ability to treat patients unresponsive to, or intolerant of, available therapy, or improved patient response over available therapy (CFR 314.500)].

FDA may grant marketing approval for a new drug product on the basis of adequate and well-controlled clinical trials establishing that the drug product has an effect on a surrogate endpoint that is reasonably likely, based on epidemiologic, therapeutic, pathophysiologic or other evidence, to predict clinical benefit or on the basis of an effect on a clinical endpoint other than survival or irreversible morbidity (CFR 314.510)).

Approval under this section will be subject to the requirement that the applicant study the drug further to verify and describe its clinical benefit, where there is uncertainty as to the relation of the surrogate endpoint to clinical benefit, or of the observed clinical benefit to ultimate outcome (CFR 314.510).

Carfilzomib Regulatory History

Investigational New Drug (IND) 071057 for carfilzomib was submitted by Proteolix in June of 2005. The drug development program for relapsed or refractory multiple myeloma was discussed during an End of Phase 1 (EOP1) meeting in March of 2007 and an End of Phase 2 (EOP2) meeting that occurred in November of 2008 in which various options were discussed for using a Phase 2 single arm trial (PX-171-003-A1, Study 3) to support a marketing application through the accelerated approval pathway.

During the EOP1 and EOP2 meetings in, the FDA provided the following advice to the Applicant regarding their proposal to use a single arm Phase 2 study (Study 3) in heavily pre-treated patients with multiple myeloma to support a request for marketing application via the accelerated approval pathway:

The determination of what constitutes available therapy for a particular population is made at the time of the regulatory action on an NDA. You have not addressed the availability of other drugs which have received regular approval for MM (multiple myeloma) such as melphalan and carmustine. Whether the results of a single arm trial will support accelerated approval will also depend on the magnitude of response, duration of response, and the risk-benefit assessment.

Carfilzomib was granted orphan drug designation for multiple myeloma in January 2008. In October of 2009, Proteolix was acquired by Onyx Pharmaceuticals. In January of 2010 an agreement was reached between Onyx and the FDA following a Special Protocol Assessment for a randomized Phase 3 comparison of lenalidomide/dexamethasone with or without carfilzomib (PX-171-009). In this trial, carfilzomib was to be given at the 20 (Cycle 1)/27 (Cycle 2 and thereafter) mg/m^2 dose using a 2-10 minute bolus infusion. The Applicant proposed to use this trial to confirm any clinical benefit shown in a single arm Phase 2 study (Study 3) following an accelerated approval. Pre-NDA meetings were held in August and September of 2010. Fast Track was granted in January of 2011. The NDA was received as a rolling submission beginning in January of 2011. The application (NDA 202714) was filed on November 26, 2011.

3. Efficacy

Study Design

The following is a summary of the design features of Study 3 that the Applicant has proposed as the primary efficacy study to support the request for accelerated approval in NDA 202714. Study 3 was conducted in over 30 sites in the USA and Canada.

Title

The title of the study is *An Open-label, Single-arm, Phase 2 Study of Carfilzomib in Patients with Relapsed and Refractory Multiple Myeloma*.

Design

The study design is a single arm clinical trial enrolling 266 patients.

Study Population

Key Inclusion Criteria

1. Measurable disease, defined as one or both of the following:
    - Serum M-protein ≥ 1 g/dl
    - Urine M-protein ≥ 200 mg/24 hr
2. Evidence of response to a previous treatment (i.e., achieved a 25% or greater reduction in M-protein for 6 weeks or greater (minimal response (MR)) to at least 1 of their prior treatment regimens
3. Refractory to the most recently received therapy. Refractory disease was defined as ≤ 25% response, or progression during therapy or within 60 days after completion of therapy
4. Subjects must have received ≥ 2 prior regimens for relapsed disease. Induction therapy and stem cell transplant (± maintenance) were to be considered as one regimen.
5. Subjects must have received prior treatment with bortezomib, and either thalidomide or lenalidomide
6. Subjects must have received an alkylating agent either alone or in combination with other multiple myeloma treatments (history of stem cell transplant was acceptable)
7. Subjects must have received an anthracycline either alone or in combination with other multiple myeloma treatments, unless not clinically indicated
8. Age ≥ 18 years of age
9. Life expectancy of more than 3 months
10. ECOG Performance Status of 0–2
11. Adequate hepatic function, with bilirubin < 2.0 times the upper limit of normal, and AST and ALT < 3.0 times the upper limit of normal
12. Absolute neutrophil count ≥ 1,000/mm^3, hemoglobin ≥ 8.0 g/dl, and platelet count ≥ 50,000/mm^3
    - Subjects were to be platelet transfusion independent
    - Screening ANC was to be independent of G-CSF or GM-CSF support for ≥ 1 week and pegylated G-CSF for ≥ 2 weeks

- Subjects could receive red blood cell or platelet transfusions or receive supportive care such as erythropoietin and darbepoetin in accordance with institutional guidelines

13. Calculated or measured creatinine clearance (CrCl) of ≥ 30 ml/min.

Key Exclusion Criteria

1. Multiple myeloma IgM
2. Primary refractory disease (Subjects who failed to achieve at least a confirmed MR [≥ 25% reduction in M-protein for ≥ 6 weeks] on any of their prior treatment regimens)
3. Non-secretory multiple myeloma, defined as < 1 g/dl M-protein in serum and < 200 mg/24 hr M-protein in urine
4. Disease measurable only by serum free light chain analysis
5. Glucocorticoid therapy (prednisone > 10 mg/day or equivalent) within the last three weeks
6. POEMS syndrome
7. Plasma cell leukemia
8. Chemotherapy with approved or investigative anticancer therapeutics including steroid therapy within the 3 weeks prior to first dose
9. Radiation therapy or immunotherapy in the previous four weeks; localized radiation therapy within 1 week prior to first dose
10. Participation in an investigational therapeutic study within 3 weeks or within 5 drug half-lives prior to first dose, which ever time was greater
11. Concurrent treatment-related myelodysplastic syndrome
12. Significant neuropathy (Grade 3, 4, or Grade 2 with pain) at the time of study initiation
13. Subjects with known or suspected amyloidosis

Treatment

Patients received carfilzomib by intravenous (IV) bolus over 2-10 minutes at 20 mg/m^2 on days 1, 2, 8, 9, 15 and 16 of the 28 days of Cycle 1, and by a 2-10 minute IV bolus at 27 mg/m^2 on days 1, 2, 8, 9, 15 and 16 of the 28 days of Cycle 2 and following cycles.

Due to the observation of fever, chills, facial edema, vomiting, weakness, confusion, shortness of breath, hypotension, syncope, chest tightness and angina during or shortly after the infusion of carfilzomib in early studies in some patients, the Applicant modified the protocol to require that dexamethasone (4 mg orally or intravenously) be administered prior to each carfilzomib administration in Cycles 1 and 2, and thereafter, at the discretion of the investigator in order to reduce the intensity of infusion reactions to carfilzomib. IV or oral fluids were also given prior to and after each carfilzomib administration. This toxicity of carfilzomib has been designated as “first dose effect” by the Applicant.

Safety Monitoring
Patients were evaluated for adverse events at the start of each cycle and prior to the administration of each dose of carfilzomib. Adverse events were scored using the NCI-CTCAE version 3.0 grading scale.

Dose Modifications
Hematologic Toxicities
Carfilzomib was to be withheld in the event of Grade 3 neutropenia, Grade 4 thrombocytopenia and Grade 4 lymphopenia persisting for > 14 days that was not pre-existing.

Non-Hematologic Toxicities
Carfilzomib was to be withheld for ≥ Grade 3 events until resolved to ≤ Grade 1 or return to baseline.

Efficacy Evaluation
The primary endpoint for this trial was Overall Response Rate (ORR) as assessed by an Independent Response Review Committee (IRC). ORR was defined as stringent Complete Response (sCR), Complete Response (CR), Very Good Partial Response (VGPR), or Partial Response (PR) according to the International Uniform Response Criteria for Multiple Myeloma assessment criteria (Durie BGM, Harousseau JL, Miguel JS, et al. International uniform response criteria for multiple myeloma. Leukemia 20: 1467-1473, 2006).

Key secondary endpoints included: Duration of response (DOR) per IRC, clinical benefit (sCR, CR, VGPR, PR, and MR), progression-free survival (PFS), time to progression (TTP), overall survival (OS), and safety.

Response status was assessed on Day 15 of Cycle 1, and Day 1 of Cycles 2-12 using the following tests: serum M-protein, urine M-protein, serum and urine M-protein by SPEP and UPEP, and Serum Free Light Chains (SFLC).

In order to confirm response, the following steps were taken: two consecutive assessments of ORR were made, evaluation of any plasmacytomas present at baseline, and a bone survey for new bony lesions. In addition to the above, to confirm a CR or sCR, the following were required: serum and urine immunofixation showing absence of the M protein, bone marrow biopsy showing < 5% plasma cells, disappearance of any soft tissue plasmacytomas, and an unscheduled SFLC draw.

Statistical Analysis Plan
Summary statistics were to be provided for the primary and secondary efficacy endpoints and for safety endpoints. For continuous variables, descriptive statistics were calculated. For discrete data, the frequency and percent distribution were presented. The primary analysis of efficacy was determined by the IRC.

Study Results

Patient Demographics

The demographic and baseline parameters, and baseline disease characteristics of the 266 patients enrolled onto Study 3 are presented below in Tables 2, 3, and 4. Several of these features are favorable: 87 % were ECOG PS 0-1, 60% had normal or favorable cytogenetics, and 67% had a beta-2 microglobulin level < 5.5 mg/L. Many of the features were unfavorable: patients had a mean of 5.4 prior therapies, 74% of patients had been treated with an autologous transplant, and 95% of patients were judged as refractory to their most recent therapy.

Table 2. Demographic Parameters of Patients Enrolled in Study 3

Demographic Parameter	Patients N = 266 n (%)
Age (years)	Median = 63.0, Range = 37, 87
Age group (years)	<65 = 146 (55), ≥65 = 120 (45)
Gender	Female = 111 (42) Male = 155 (58)
Race	African American = 53 (20) Asian/Pacific Islander = 6 (2) Caucasian = 190 (71) Hispanic = 10 (4) Other = 7 (3)
ECOG PS	0 = 69 (26) 1 = 162 (61) 2 = 35 (13)

Table 3. Baseline Parameters for Patients Enrolled in Study 3

Baseline Parameter	N=266
Time from diagnosis (years)	Median = 5.4 Range = 0.5, 22.3
Number of prior therapies	Mean = 5.4 Median = 5.0 Range = 1, 20
Prior transplant	198 patients (74%)
Refractory to most recent therapy	Refractory = 252 patients (95%)* Not refractory = 14 patients (5%)

*Refractory was defined as:
1. Progression during most recent therapy 198 patients (74%)
2. Progression < 60 days after most recent therapy = 38 patients (14%)
3. ≤ 25% response to treatment = 16 (2.3)

Table 4. Baseline Disease Characteristics of Patients Enrolled in Study 3

Baseline Parameter	Patients N=266 n (%)
Cytogenetics or FISH	Normal/Favorable = 159 (60), Poor Prognosis* = 75 (28) Unknown/Not tested = 32 (12)
Beta-2 Microglobulin	<5.5 mg/l = 178 (67) ≥5.5 mg/ml = 81 (31) Unknown/Not tested = 7 (3)
Bone Marrow Plasma Cell Involvement	< 50% = 143 (54) ≥ 50% = 106 (40) Unknown/Not tested = 17 (6)

*The markers for poor prognosis were the following: t(4;14), t(14;16), deletion(17p;13) by cytogenetics/FISH or deletion (13q;14) by cytogenetics.

Summary of Disposition, Duration of Treatment and Protocol Violations in Study 3
The protocol violations from Study 3 are summarized in Table 5 below. The total number of protocol deviations was 44%. The types of violations are also listed in Table 5. Most of the protocol violations were related to inclusion/exclusion criteria (19%), missed doses for a reason that was other than an adverse event (9%), and missed laboratory assessments (27%).

Table 5. Protocol Violations in Study 3

Deviation category	Total Patients N = 266 n (%)
Enrolled patients	266 (100)
Total number of patients with any protocol deviation	118 (44)
Enrollment error (Inclusion/exclusion criteria)	51 (19)
Study drug	
Administration error/incorrect dose	2 (<1)
Missed dose (reason other than AE)	25 (9)
Missed laboratory assessment(s)	72 (27)
Excluded concomitant medication	8 (3)
Not evaluable due to missed disease assessment	9 (3)
Informed consent process error	9 (3)
Delayed withdrawal	2 (<1)

The disposition of the patients enrolled Study 3 is summarized in Table 6 below. Forty percent of patients completed twelve cycles of carfilzomib.

Table 6. Disposition and Exposure in Study 3

	Total patients N = 266 n (%)
Enrolled patients	266 (100)
Patients treated	266 (100)
Completed 12 cycles of study drug	40 (15)
Number of Patients Starting Cycles	
1	266 (100)
2	215 (80)
3	169 (64)
4	146 (55)
5	120 (45)
6	97 (37)
7	83 (31)
8	73 (27)
9	65 (24)
10	58 (22)
11	50 (19)
12	42 (16)
≥13	7 (3)
Duration on treatment (days)	
Mean (SD)	134 (122)
Median	91.5
Range	1, 514

Exposure to Available Therapy for Multiple Myeloma

Accelerated approval applies to certain new drug products that have been studied for their safety and effectiveness and treating serious or life-threatening illnesses and that provide meaningful therapeutic benefit to patients over existing treatments [e.g., ability to treat patients unresponsive to, or intolerant of, available therapy, or improved patient response over available therapy (CFR 314.500)].

Therefore, it is important to analyze the prior treatment history of each patient entered onto the primary efficacy Phase 2 study (Study 3), and to determine whether each patient had been documented to be unresponsive to or intolerant of each of the drugs which have been approved by the FDA as therapy for multiple myeloma. The prior exposure of the 266 patients entered onto Study 3 to each of the approved agents for multiple myeloma is shown in Table 7. Of the 266 patients enrolled in the study, 35.7% never received anthracyclines, 24.2% never received cyclophosphamide, 15.4% never received melphalan, and only 1.9% of patients were exposed to carmustine.

Table 7. Prior Exposure to Approved Agents of Patients Entered onto Study 3

FDA Approved Product	Exposed Patients N = 266	
	n	(%)
Bortezomib	265	(99.6)
Lenalidomide	249	(93.6)
Thalidomide	199	(74.8)
Anthracycline (any)	171	(64.3)
Cyclophosphamide	175	(65.8)
Melphalan	225	(84.6)
Carmustine	5	(1.9)

The number of patients entered on the study who had been documented to be unresponsive or intolerant of each of the FDA approved agents is shown in Table 8. Although 86.8% of patients were documented to be unresponsive or intolerant to both bortezomib and lenalidomide, only 56% were documented to be unresponsive or intolerant to thalidomide, and only a minority of patients had been shown to be unresponsive or intolerant to anthracyclines (36.8%), cyclophosphamide (34.6%), or melphalan (28.9%).

Table 8. Patients Documented to be Unresponsive/Intolerant to Approved Therapies*

FDA Approved Product	Unresponsive/Intolerant Patients N = 266	
	n	(%)
Bortezomib	231	(86.8)
Lenalidomide	231	(86.8)
Thalidomide	148	(56.0)
Anthracycline (any)	98	(36.8)
Cyclophosphamide	92	(34.6)
Melphalan	77	(28.9)
Carmustine	1	(<1)

*FDA Analysis of Applicant's Data Sets

Primary Efficacy Analysis by Applicant

The primary efficacy endpoint was the overall response rate (ORR) as determined by an Independent Review Committee (IRC) which required confirmation on at least 2 consecutive evaluations. As shown below in Table 9, the Applicant stated that the ORR was 22.9% when computed on the basis of all treated patients (N=266). All responses were confirmed.

Table 9. Applicant's Efficacy Analysis for the Primary Endpoint (ORR)

Study Population	n/N	%
ORR in ITT* Population	61/266	22.9%

*ITT=intent to treat population

Primary Efficacy Analysis by FDA

As shown below in Table 10, the FDA analyzed ORR among patients documented to be unresponsive or intolerant to bortezomib alone (Group 1), documented to be unresponsive or intolerant to bortezomib and lenalidomide (Group 2), documented to be unresponsive or intolerant to bortezomib, lenalidomide and anthracyclines (Group 3), or documented to be unresponsive or intolerant to bortezomib, lenalidomide, anthracyclines and either melphalan or cyclophosphamide or with a history of hematopoietic stem cell transplant (Group 4). The ORR in these groups was found to be: 20.8%, 20.2%, 22.1%, and 23.2% respectively.

Table 10. FDA Analysis of Patients Unresponsive to Approved Agents (Based on N=266 Patients)

Patient Population	n/N	(%)	(95% CI)
Intent to Treat Population	61/266	(22.9)	(18%, 28.5)
Group1 Unresponsive or Intolerant to: • Bortezomib	48/231	(20.9)	(15.7%, 26.6%)
Group 2 Unresponsive or Intolerant to: • Bortezomib • Lenalidomide	42/208	(20.2)	(15.0%, 26.3%)
Group 3 Unresponsive or Intolerant to: • Bortezomib • Lenalidomide • Anthracycline	17/77	(22.1)	(13.4%, 33.0%)
Group 4 Unresponsive or Intolerant to: • Bortezomib • Lenalidomide • Anthracycline • Melphalan, Cyclophosphamide, or history of transplant	16/69	(23.2)	(13.9%, 34.9%)

Efficacy Results As Measured by Secondary Endpoints

Duration of Response

The Applicant carried out an analysis of duration of response (DOR) (see Table 11 below) and concluded that the median DOR was 7.8 months. The duration of response was defined by the Applicant as the time interval between the date of the first evaluation at which a response (sCR, CR, VGPR, or PR) was established, and the date of the evaluation at which progression was established.

Table 11. Applicant's Analysis of Duration of Response

Responders N = 61	Median DOR (months)	95% CI (months)
All Responders	7.8	6.5, 9.7

The FDA has re-analyzed the data submitted by the Applicant to establish the duration of response as defined by the time interval between the date of the first evaluation on which the response was established, and the date of the last evaluation on which the response persisted, prior to the evaluation on which evidence of progression occurred. The result of these analyses, which are presented below in Table 12, leads to the estimate of a median duration of response of 6.5 months.

Table 12. FDA Analysis of Duration of Response

Responders N=61	Median DOR (months)	95% CI (months)
All Responders	6.5	4.6, 8.3

FDA analyzed the duration of response for the various groups of responders based on documented unresponsiveness or intolerance to prior therapies (Table 10) using both the Applicant's method of calculating DOR and the alternate method used by FDA. These results are in Tables 13 and 14.

Table 13. FDA Analysis of Applicant's Duration of Response for Patients Unresponsive to Agents Which was Presented in Table 10

Responder Group	Median DOR (months)	95% CI (months)
Group 1 Unresponsive or Intolerant to: • Bortezomib	7.8	(5.6, 9.2)
Group 2 Unresponsive or Intolerant to: • Bortezomib • Lenalidomide	7.4	(5.6, 8.4)
Group 3 Unresponsive or Intolerant to: • Bortezomib • Lenalidomide • Anthracycline	8.3	(6.5, 9.2)
Group 4 Unresponsive or Intolerant to: • Bortezomib • Lenalidomide • Anthracycline • Melphalan, Cyclophosphamide, or with a history of transplant	8.3	(6.7, 9.2)

Table 14. FDA Analysis of FDA Duration of Response for Patients Unresponsive to Agents Which was Presented in Table 10

Responder Group	Median DOR (months)	95% CI (months)
Group 1 Unresponsive or Intolerant to: • Bortezomib	6.5	(4.6, 8.3)
Group 2 Unresponsive or Intolerant to: • Bortezomib • Lenalidomide	6.5	(5.6, 8.3)
Group 3 Unresponsive or Intolerant to: • Bortezomib • Lenalidomide • Anthracycline	7.4	(5.6, 8.3)
Group 4 Unresponsive or Intolerant to: • Bortezomib • Lenalidomide • Anthracycline • Melphalan, Cyclophosphamide, or with a history of transplant	7.4	(5.8, 8.3)

Steroid Use

As noted previously, an uncertainty in this study is whether the regular use of dexamethasone has confounded the interpretation of the treatment effect of carfilzomib. The applicant has reported that dexamethasone was necessary in order to reduce infusion toxicities associated with the carfilzomib infusion. Patients were required to receive dexamethasone (4 mg orally or by IV) prior to all carfilzomib doses during the first cycle and prior to all carfilzomib doses during the first dose escalation (27 mg/m^2) cycle. After that, dexamethasone use was optional and was restarted in patients with continued toxicities associated with carfilzomib infusion. Dexamethasone is routinely given either alone or with other therapies to treat patients with multiple myeloma. These doses typically are 160 mg/cycle (considered low-dose dexamethasone) to 480 mg/cycle (considered high-dose dexamethasone) range. Although the maximum dose of dexamethasone a patient would receive per cycle in the carfilzomib efficacy study, Study 3, is lower (24 mg/cycle), a therapeutic effect cannot be ruled out in a single arm trial. In Study 3, the actual treatment effect of carfilzomib is confounded by the concomitant use of dexamethasone in the study and the response rates may be lower in the absence of steroids.

4. Safety

Overview of the Safety Population

The entire safety database consists of 768 patients who were exposed to at least one dose of carfilzomib. Some (156) of the 768 patients were patients with solid tumors or hematological diseases besides multiple myeloma (20%) while the majority (612) of patients had multiple myeloma (80%). The data included in the safety data base were

from multiple Phase 1 (86 patients) and Phase 2 (526 patients) trials as shown below in Table 15. For the Safety Analyses, FDA chose to focus on the population of 526 patients with multiple myeloma who were enrolled on Phase 2 studies and the 266 patients who were enrolled on Study 3, the primary efficacy study. The inclusion of patients from Phase 1 studies would introduce a wide range of drug exposures and treatment durations. These factors may alter the incidence of adverse events and others safety variables.

Table 15. Clinical Trials Contained in the Integrated Summary of Safety

Trial	Phase	Patients (All)	Patients (MM*)
PX-171-001	1	29	10
PX-171-002	1	48	28
PX-171-003 Part 1	2	46	46
PX-171-003 Part 2	2	266	266
PX-171-004 Part 1	2	35	35
PX-171-004 Part 2	2	129	129
PX-171-005	2	50	50
PX-171-006	1b	40	40
PX-171-007	1b/2	108	8
PX-171-008	1b	17	0
Total		**768**	**612 (86 P1 + 526 P2)**

*MM=multiple myeloma

Safety Population Demographics

The demographical features of the 526 patients with multiple myeloma entered in Phase 2 trials are presented in Table 16. The median age of the patients with multiple myeloma enrolled in Phase 2 was 64 years. Eighty-eight percent of the patients had an ECOG PS of 0-1.

Table 16. Demographics of Patients with Multiple Myeloma Enrolled in Phase 2 Studies

		Patients N = 526 n (%)
Age (years)	Mean	63
	Median	64
	Range	37, 87
Age group (years)	<65	279 (53)
	≥65	247 (47)
Gender	Female	224 (43)
	Male	302 (57)
Race	African American	97 (18)
	Asian/Pacific Islander	19 (4)
	Caucasian	381 (72)
	Hispanic	18 (3)
	Other	11 (2)
ECOG PS	0	156 (30)
	1	301 (58)
	2	61 (12)
	ND	2 (<1)

*ND = Not done

Exposure

As shown below in Table 17, 278 (53%) of the 526 patients with multiple myeloma enrolled in Phase 2 trials received the dose and schedule used in the primary efficacy study (20 mg/mg/m^2 for the first cycle and 27 mg/m^2 for succeeding cycles), 198 (38%) patients received carfilzomib at the 20 mg/m^2 dose only, and 50 (10%) patients were exposed to carfilzomib at the 15/20/27 mg/m^2 dosing regimen. A tabulation of exposure to carfilzomib (as measured by weeks of treatment) is presented in Table 18.

Table 17. Distribution of Doses of Carfilzomib Administered to Patients with Multiple Myeloma Enrolled in Phase 2

Dose (mg/m^2)	Patients N = 526 n (%)
20/27	278 (53)
20	198 (38)
15/20/27	50 (10)

Table 18. Exposure to Carfilzomib as Measured by Weeks of Treatment

	Weeks of treatment
Mean (SD)	21.2 (17.8)
Median	15.1
Min, Max	0, 90

Deaths on Study and Within 30 days of Last Dose of Carfilzomib
On study deaths are defined as those deaths occurring during treatment with carfilzomib and within 30 days after the last dose. The on study deaths for patients with multiple myeloma entered on Phase 2 studies (N=526), and for Study 3 (N=266) are presented below in Tables 19 and 20 respectively.

The most frequent cause of death among the patients with multiple myeloma enrolled in Phase 2 studies was progression of disease. However, the most frequent cause of death not due to progressive disease was cardiac adverse events. The Applicant identified 5 deaths attributable to cardiac causes. The FDA analysis of on study deaths in this population identified an additional 2 cases that were associated with a cardiac cause of death and an additional 3 cases where cardiac causes may have played a role in the death of the patients. In addition to the deaths associated with cardiac causes, there were 2 hepatic deaths (Table 19).

Table 19. On Study Deaths for Patients with Multiple Myeloma Enrolled in Phase 2 Studies

Cause of Death	Primary Cause of Death (N = 526) n (%)
Disease Progression	21 (4)
Cardiac (Identified by Applicant and FDA)	5 (1)
Cardiac (Identified by FDA)	2* (<1)
Cardiac possibly contributory to death (Identified by FDA)	3** (<1)
Hepatic Failure	2 (<1)
Multi-Organ Failure	2 (<1)
Sepsis	2 (<1)
Hemorrhage intracranial	1 (<1)
Pneumonia	1 (<1)
Renal Failure	1 (<1)
Unknown	1 (<1)
Total	38 (7)

*3-09-218: Applicant listed cause of death as *Dyspnea*, 3-16-491: Applicant listed cause of death as *Disease Progression*
**These 3 cases are represented in 2 places in Table 23, but counted once for the total deaths (3-15-432: Applicant listed cause of death as *Sepsis*, 3-16-495 Applicant listed cause of death as *Disease Progression*, 3-16-778: Applicant listed cause of death "*Unknown*")

As shown in Table 20, the majority of the on study deaths occurred among patients enrolled in the primary efficacy study (Study 3). Four of the five cardiac deaths identified by both the Applicant and FDA, the 2 additional cardiac deaths identified by the FDA, 3 of the 4 deaths associated with cardiac causes, and both of the hepatic deaths occurred on Study 3.

Table 20. On Study Deaths for Study 3

Cause of Death	Primary Cause of Death (N = 266) n (%)
Disease progression	12 (5)
Cardiac (Identified by Applicant and FDA)	4 (2)
Cardiac (Identified by FDA)	2* (<1)
Cardiac possibly contributory to death (Identified by FDA)	3** (1)
Hepatic failure	2 (<1)
Hemorrhage intracranial	1 (<1)
Pneumonia	1 (<1)
Sepsis	1 (<1)
Unknown	1 (<1)
Total	24 (9)

*3-09-218: Applicant listed cause of death as *Dyspnea*, 3-16-491: Applicant listed cause of death as *Disease Progression*
**These 3 cases are represented in 2 places in Table 23, but counted once for the total deaths (3-15-432: Applicant listed cause of death as *Sepsis*, 3-16-495 Applicant listed cause of death as *Disease Progression*, 3-16-778: Applicant listed cause of death "*Unknown*")

Discontinuations of Carfilzomib Associated with Toxicity

The major reasons for study drug discontinuation for the patients with multiple myeloma enrolled in Phase 2 studies are shown by Organ Class (Table 21) and by Preferred Term (Table 22). In Table 21, the most common class for discontinuations was General Disorders which includes the preferred term for Disease Progression. The two organ class categories that had the most adverse events leading to discontinuation of carfilzomib were Cardiac Disorders 30/526 (6%) and Respiratory Disorders 22/526 (4%).

Table 21. Discontinuations in Patients with Multiple Myeloma in Phase 2 Studies due to an Adverse Event (Shown in Decreasing Order by Organ Class)

Organ Class	N=526* n (%)
General disorders and administration site conditions	42 (8)
Cardiac disorders	30 (6)
Respiratory, thoracic and mediastinal disorders	22 (4)
Infections and infestations	20 (4)
Nervous system disorders	17 (3)
Renal and urinary disorders	14 (3)
Metabolism and nutrition disorders	12 (2)
Musculoskeletal and connective tissue disorders	11 (2)
Blood and lymphatic system disorders	10 (2)
Investigations	10 (2)
Psychiatric disorders	7 (1)
Gastrointestinal disorders	6 (1)
Skin and subcutaneous tissue disorders	6 (1)
Hepatobiliary disorders	3 (<1)
Neoplasms benign, malignant and unspecified	3 (<1)
Vascular disorders	3 (<1)
Endocrine disorders	1 (<1)
Eye disorders	1 (<1)
Immune system disorders	1 (<1)
Reproductive system and breast disorders	1 (<1)

*Patients may be counted in more than 1 organ class

Table 22 lists the most common adverse events leading to discontinuation of carfilzomib. Aside from adverse events due to disease progression, the major adverse events leading to discontinuations of carfilzomib in these categories were dyspnea, pneumonia, congestive heart failure. There were additional patients who discontinued carfilzomib due to a cardiac arrest.

Table 22. Discontinuations* in Patients with Multiple Myeloma Enrolled in Phase 2 Studies due to an Adverse Event (Shown in Decreasing Order by Preferred Term, ≥ 1% of Patients)

Preferred Term	N=526** n (%)
Dyspnea	10 (2)
Pneumonia	10 (2)
Cardiac failure congestive	9 (2)
Renal failure acute	9 (2)
Blood creatinine increased	7 (1)
Pyrexia	6 (1)
Cardiac arrest	5 (1)
Thrombocytopenia	5 (1)

*Excluding terms attributed to progressive multiple myeloma disease (disease progression, hypercalcemia, spinal cord compression)

**Patients may be counted in more than 1 term.

Serious Adverse Events (SAEs) Among 526 Patients with Multiple Myeloma in the Phase 2 Studies

As shown in Table 23 below, pulmonary and cardiac toxicities also contributed to serious adverse events among the 526 patients with multiple myeloma enrolled in Phase 2 studies. There were 42 (8%) patients who experienced a cardiac SAE and 36 (7%) patients experienced a pulmonary toxicity. The majority of these were Grade 3 or 4 toxicities. As with the patients who discontinued carfilzomib due to toxicity, the major SAEs were congestive heart failure and cardiac arrest. Dyspnea was the most frequent pulmonary toxicity leading to discontinuation of carfilzomib and the most frequent pulmonary SAE.

Table 23. Cardiac, Pulmonary, and Hepatic SAEs for Patients with Multiple Myeloma Enrolled in Phase 2 Studies (N=526)

System Organ Class Preferred Term	**Grade 1 to 5** **n (%)**	**Grade 3 or 4** **n (%)**
Cardiac disorders	**42 (8)**	**36 (7)**
Cardiac failure congestive	18 (3)	17 (3)
Cardiac arrest	5 (1)	2 (<1)
Atrial fibrillation	4 (<1)	4 (<1)
Myocardial ischemia	3 (<1)	2 (<1)
Atrial flutter	2 (<1)	1 (<1)
Cardiac failure	2 (<1)	2 (<1)
Ventricular dysfunction	2 (<1)	2 (<1)
Acute coronary syndrome	1 (<1)	1 (<1)
Acute myocardial infarction	1 (<1)	1 (<1)
Aortic valve stenosis	1 (<1)	1 (<1)
Arrhythmia	1 (<1)	1 (<1)
Cardiac disorder	1 (<1)	0 (0)
Cardiomyopathy	1 (<1)	1 (<1)
Congestive cardiomyopathy	1 (<1)	1 (<1)
Mitral valve incompetence	1 (<1)	1 (<1)
Right ventricular failure	1 (<1)	1 (<1)
Supraventricular tachycardia	1 (<1)	1 (<1)
Respiratory, thoracic and mediastinal disorders	**36 (7)**	**21 (4)**
Dyspnea	12 (2)	10 (2)
Pulmonary embolism	6 (1)	5 (1)
Pulmonary edema	5 (1)	4 (<1)
Pleural effusion	4 (<1)	3 (<1)
Respiratory failure	3 (<1)	3 (<1)
Hemoptysis	2 (<1)	1 (<1)
Hypoxia	2 (<1)	2 (<1)
Acute pulmonary edema	1 (<1)	1 (<1)
Acute respiratory failure	1 (<1)	1 (<1)
Chronic obstructive pulmonary disease	1 (<1)	0 (0)
Cough	1 (<1)	0 (0)
Pneumonia aspiration	1 (<1)	1 (<1)
Pneumonitis	1 (<1)	1 (<1)
Pulmonary alveolar hemorrhage	1 (<1)	1 (<1)
Pulmonary hypertension	1 (<1)	1 (<1)
Respiratory alkalosis	1 (<1)	1 (<1)
Hepatobiliary disorders	**3 (<1)**	**8 (2)**
Hepatic failure	2 (<1)	0 (0)
Venoocclusive liver disease	1 (<1)	1 (<1)

The patients in Study 3 also experienced cardiac and pulmonary SAEs at similar rates in Study 3 (Table 24), the primary efficacy study as in the larger population of 526 patients with multiple myeloma enrolled in Phase 2 studies.

Table 24. SAEs for Patients with Multiple Myeloma Enrolled in Study 3 (Shown in Decreasing Order by Organ Class)

Organ Class	N=266 n (%)
Infections and infestations	18 (7)
Cardiac disorders	11 (4)
Respiratory, thoracic and mediastinal disorders	11 (4)
General disorders and administration site conditions	8 (3)
Nervous system disorders	8 (3)
Gastrointestinal disorders	6 (2)
Investigations	5 (2)
Metabolism and nutrition disorders	5 (2)
Musculoskeletal and connective tissue disorders	4 (2)
Renal and urinary disorders	4 (2)
Blood and lymphatic system disorders	3 (1)
Psychiatric disorders	3 (1)
Vascular disorders	3 (1)
Endocrine disorders	1 (<1)
Eye disorders	1 (<1)
Hepatobiliary disorders	1 (<1)
Immune system disorders	1 (<1)
Injury, poisoning and procedural complications	1 (<1)
Neoplasms benign, malignant and unspecified	1 (<1)

*Patients may be counted in more than 1 organ class

Adverse Events:

The frequency of adverse events among the patients with multiple myeloma entered on Phase 2 trials (N=526) is summarized by organ class in Table 25. Seventy percent of patients experienced a respiratory adverse event. Twenty-three percent of these patients experienced a toxicity associated with cardiac disorders.

Table 25. AEs by Organ Class for 526 Patients with Multiple Myeloma Enrolled in Phase 2 Studies

System Organ Class	All Grades n (%)
General disorders and administration site conditions	450 (86)
Gastrointestinal disorders	407 (77)
Blood and lymphatic system disorders	373 (71)
Respiratory, thoracic and mediastinal disorders	370 (70)
Metabolism and nutrition disorders	356 (68)
Musculoskeletal and connective tissue disorders	352 (67)
Investigations	343 (65)
Nervous system disorders	332 (63)
Infections and infestations	332 (63)
Skin and subcutaneous tissue disorders	188 (36)
Psychiatric disorders	179 (34)
Vascular disorders	150 (29)
Cardiac disorders	123 (23)
Renal and urinary disorders	120 (23)
Eye disorders	79 (15)
Injury, poisoning and procedural complications	65 (12)
Reproductive system and breast disorders	33 (6)
Neoplasms benign, malignant and unspecified	28 (5)
Ear and labyrinth disorders	24 (5)
Surgical and medical procedures	17 (3)
Hepatobiliary disorders	16 (3)
Immune system disorders	14 (3)
Endocrine disorders	8 (2)

*Patients may be counted in more than 1 organ class

The adverse events that occurred in patients with multiple myeloma enrolled in Phase 2 studies are presented in Table 26. Dyspnea occurred in 35% of patients.

Table 26. AEs by Preferred Term for 526 Patients with Multiple Myeloma Enrolled in Phase 2 Studies

Preferred Term	All Grades N=526		Grade 3 and 4 N=526	
	n	(%)	n	(%)
Fatigue	300	(57)	41	(8)
Anemia	267	(51)	128	(24)
Nausea	244	(46)	8	(2)
Thrombocytopenia	197	(38)	125	(24)
Dyspnea	186	(35)	26	(5)
Diarrhea	179	(34)	5	(1)
Pyrexia	163	(31)	9	(2)
Headache	150	(29)	7	(1)
Upper respiratory tract infection	149	(28)	17	(3)
Cough	140	(27)	1	(<1)
Lymphopenia	132	(25)	100	(19)
Blood creatinine increased	132	(25)	14	(3)
Edema peripheral	131	(25)	3	(<1)
Vomiting	120	(23)	6	(1)
Neutropenia	118	(22)	59	(11)
Constipation	114	(22)	1	(<1)
Back pain	113	(22)	18	(<1)
Insomnia	98	(19)	0	(0)
Arthralgia	90	(17)	9	(<1)
Chills	84	(16)	1	(<1)

Discussion of Attribution of the Causes of Organ Specific Adverse Events in Single Arm Trials

Small single arm studies cannot be used to distinguish the causes of adverse events as due to the effect of the test drug as opposed to adverse events due to patient and disease related factors. Distinguishing the drug effect from the disease is best done through the analysis of data from well designed randomized controlled trials where the drug effect can be isolated. In general, the cause of adverse events from single arm trials where the drug effect is unknown must be assigned to the experimental therapy. Among the safety population of patients with multiple myeloma enrolled in Phase 2 studies, there are several organ systems in which a higher incidence of adverse events has occurred than would be expected in this population of patients with multiple myeloma including cardiac, pulmonary, and hepatic toxicities, which must be assigned to carfilzomib. In addition to significant life threatening adverse events associated with the heart, lung and liver, a separate and distinct set of adverse events were associated with the infusion of carfilzomib.

Cardiac Toxicity

A great variety of cardiac adverse events were reported in Phase 2 studies as shown in Table 27. Cardiac on study deaths occurred in a number that was higher than other organ specific causes of on study deaths (see Table 19 and Table 20). The causes of death for the 5 patients whose on study deaths were associated with cardiac causes were: acute coronary syndrome (1), cardiac arrest (3), and cardiac disorder (1). In addition, one

patient (3-09-218) who had dyspnea listed as the cause of death by the Applicant, may have died from complications of congestive heart failure. Another patient (3-16-491) who was listed by the Applicant as having died of disease progression may have died of congestive heart failure.

The timing of the on study cardiac deaths in relationship to carfilzomib dosing of these 6 patients identified by the FDA as on study cardiac deaths is summarized below in Table 27. Most of these patients died in Cycle 1 or Cycle 2 and three of these patients died within 2 days of the last dose, indicating a direct toxic effect of carfilzomib on the heart in these patients. Patient 3-15-441 has a cardiac arrest within hours of the last dose. FDA has identified 3 additional patients for which cardiac causes may have been the cause of death. Patient 3-15-432 had two cardiac arrests in the setting of sepsis, 3 days after the last dose of carfilzomib. Patient 3-16-495 had a cardiac arrest 3 days after the last dose of carfilzomib, and Patient 3-16-778 was found dead at home 6 days after the last dose of carfilzomib.

Table 27. Summary of Cardiac Deaths

Patient ID	Age (years)	Cardiac History	Death Occurred			CHF or Arrest
			Cycle	Days After Last Dose	Total Doses	
3-08-086	50	CAD/CABG DM ↑lipids	1	18	4	Arrest
3-09-218*	65	HTN	2	22	12	CHF
3-09-220	83	CAD ↑lipids	1	3	2	Arrest
3-11-255	66	HTN	4	1	21	Arrest
3-15-441	53	DM ↑lipids	1	<1**	4	Arrest
3-16-491*	72	HTN	1	8	2	CHF
4-06-156	52	↑lipids	1	1	2	Arrest

*Identified by FDA
**Death occurred within hours of the last dose.
CAD = Coronary artery disease, CABG = Coronary bypass graft, CHF = Congestive heart failure, DM = Diabetes Mellitus, HTN = hypertension, ↑lipids = hyperlipidemia,

Carfilzomib was discontinued for cardiac disorders in 5.7% of the 526 patients with multiple myeloma enrolled in Phase 2 studies (Table 21). Among these were discontinuations for congestive heart failure in 9 patients and cardiac arrest in 5 patients (Table 22). In terms of SAEs (Table 23), 42 patients experienced cardiac related SAEs. Among these, 18 patients had a SAE associated with congestive heart failure (preferred

terms: Cardiac failure congestive and Congestive cardiomyopathy), and 5 patients experienced cardiac arrest.

Nearly a quarter of the 526 patients experienced one or more cardiac adverse events as shown above in Table 25. These adverse events included thirty-seven that were Grade 3 and 10 that were Grade 4 or 5. The most frequently reported cardiac adverse events from Study 3 are summarized in Table 28.

Table 28. Cardiac Adverse Events from Patients in Study 3

Preferred Term	All grades N = 266		Grade 3 or greater N = 266	
	n	(%)	n	(%)
Dyspnea	90	(34)	9	(3)
Hypertension	39	(15)	21	(8)
Hypotension	21	(8)	6	(2)
Cardiac failure congestive	10	(4)	9	(3)
Cardiac arrest	4	(2)	4	(2)
Atrial fibrillation	5	(2)	2	(<1)
Deep vein thrombosis	5	(2)	3	(1)
Pulmonary edema	5	(2)	3	(1)
Sinus tachycardia	4	(2)	0	(<1)
Myocardial ischemia	3	(1)	2	(<1)

Pulmonary Toxicity

Over 70% of patients enrolled in Phase 2 studies reported adverse events associated with the respiratory system (see Table 25). Twenty-two patients discontinued carfilzomib because of a respiratory adverse event (see Table 21). Dyspnea and pneumonia were the most frequent pulmonary adverse events leading to carfilzomib discontinuations (see Table 22). There were 36 pulmonary SAEs (see Table 23). Reversible SAEs involving the lung were reported in 8 patients, which required hospitalization in 2 patients for stabilization. Two of these events were associated with the clinical diagnosis of pulmonary hypertension (one of which was also associated with veno-occlusive disease and the other with congestive heart failure). Of these 10 patients, carfilzomib was interrupted in 3, the dose was reduced in 1 and carfilzomib was discontinued permanently in 2.

Dyspnea was a common (35%) adverse event in the 526 multiple myeloma patients entered onto Phase 2 trials (see Table 26). The median duration of these events was 8 days. While most of these events were Grade 1 and 2 in severity, 5% were Grade 3 or 4. It is not clear whether dyspnea was associated with pulmonary toxicity, cardiac toxicity, or infusion reactions because these were single arm trials.

It is remarkable that cardiac and pulmonary toxicities were also reported in the pre-clinical toxicity studies of carfilzomib carried out by the Applicant. The pathogenesis of these cardiac and pulmonary toxicities is unknown. Monkeys administered a single bolus

intravenous dose of carfilzomib at 3 mg/kg (approximately 1.3 times recommended dose in humans of 27 mg/m^2 based on body surface area) experienced hypotension, increased heart rate, and increased serum levels of troponin-T. (Note that the bolus infusion may have been administered in a shorter time than was the case in the bolus infusion in human subjects, which was 2-10 minutes). The studies of repeated intravenous bolus administrations of carfilzomib at ≥ 2 mg/kg/dose in rats and 2 mg/kg/dose in monkeys using dosing schedules similar to those used clinically resulted in mortalities that were due to toxicities occurring in the cardiovascular and pulmonary systems. Following repeated bolus intravenous administration in monkeys at ≥ 1 mg/kg/dose, cardiovascular toxicities included myocardial degeneration, myocyte hypertrophy and inflammation. The C_{max} and significant toxicities in rats, including death, pre-renal azotemia (elevated blood urea nitrogen and creatinine), lethargy, dyspnea, observed following a single bolus injection of 8 mg/kg carfilzomib were reduced when the same dose was administered as a 30-minute infusion, while a similar level of proteasome inhibition was maintained.

Hepatic Toxicity

The distribution of deaths, SAEs and adverse events in patients with multiple myeloma associated with hepatotoxicity is presented in Table 29. Among the 526 patients with multiple myeloma who were entered in Phase 2 trials, and among the 266 patients on Study 3, there were two on-study deaths associated with hepatic failure (see Tables 19-20 and 29). Both of these individuals had normal liver function tests before being treated with carfilzomib. There were two other life threatening cases of hepatic failure which in contrast to the above two cases, were reversible, one in a 61 year old who experienced Grade 2 hepatic encephalopathy and grade 3 hepatic enzyme elevations from days 47-61 of carfilzomib therapy.

Table 29. Hepatotoxicity Among Patients with Multiple Myeloma

Event	Safety Population N=526 n (%)	Study 3 N=266 n (%)
Deaths	2 (<1)	2 (<1)
SAEs	3 (<1)	2 (<1)
Hepatic failure (Reversible)	3 (<1)	3 (1)
Veno-occlusive disease	1 (<1)	0 (0)
Laboratory criteria for Hy's Law (ALT or AST ≥ 3x ULN and total bilirubin ≥ 2x ULN)	4 (<1)	3 (1)
Hy's Law confirmed	0 (0)	0 (0)

Infusion Reactions with Carfilzomib

During the course of carfilzomib drug development, the Applicant identified symptoms and adverse events which occur within 24 hours of each administration of carfilzomib. These adverse events include: fever, chills, rigors, pyrexia, myalgias, arthralgias, dyspnea, hypotension, hypoxia and flushing. In an attempt to reduce this toxicity, the Applicant modified the clinical protocols by adding premedication with dexamethasone along with the administration of oral and intravenous hydration. In addition, the first

carfilzomib dose was always 20 mg/m^2 either for the first cycle or later on for the first two doses of Cycle 1. The etiology for this constellation of symptoms is unknown.

5. Benefit-Risk Discussion

Efficacy as Measured by the Primary Endpoint: ORR
The ORR to carfilzomib in patients with relapsed multiple myeloma was approximately 22%, whether analyzed by the Applicant or by the FDA. The number of entered patients who had been shown to be unresponsive or intolerant to 5 of the 6 groups of approved agents for multiple myeloma (excluding carmustine) was a very small fraction of the ITT population (69/266).

Safety
The safety data suggests that there are a number of patients with relapsed multiple myeloma who are at high risk of developing life-threatening cardiac toxicities due to carfilzomib. Cardiac toxicity was prominent among "On Study Deaths", adverse events contributing to discontinuation of carfilzomib, SAEs, and adverse events. In addition to the cardiac toxicities, there were significant pulmonary, and to a lesser extent hepatic toxicities and toxicities associated with carfilzomib infusion that need further characterization. As these safety signals were identified using data from a single arm study, they must be attributed to the study drug until demonstrated otherwise in a randomized controlled trial. Of note, patients with multiple myeloma treated with IMiDs do not show this pattern of cardiac, pulmonary, and hepatic toxicities.

Summary
Since carfilzomib produced an ORR of only 22% in the primary efficacy study, it may not provide an advantage over available therapy. FDA is very concerned with the severe toxicities, including deaths that are associated with the use of this agent. The pathogenesis of these toxicities is not understood. Considering these factors, the risks of carfilzomib may not outweigh its benefits.